Exhibit A

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20009WOP00	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/AU2004/001416	International filing date *(day/month/year)* 15 October 2004	Priority date *(day/month/year)* 17 October 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

A61K 38/45 (2006.01) ***A61P 35/00*** (2006.01) ***C12N 9/12*** (2006.01)

Applicant

INTER-K PTY LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **21** sheets, as follows:
      - [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15 August 2005	08 February 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **M. Ong** Telephone No. (02) 6283 2491

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001416

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-14, 16-38** as originally filed/furnished

pages* **15** received by this Authority on **19 January 2006** with the letter of 18 January 2006

pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished

pages* as amended (together with any statement) under Article 19

pages* **39-41** received by this Authority on **19 January 2006** with the letter of 18 January 2006

pages* received by this Authority on with the letter of

[X] the drawings:

pages **1/20-20/20** as originally filed/furnished

pages* received by this Authority on with the letter of

pages* received by this Authority on with the letter of

[X] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify)*:

[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify)*:

[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [ ] in electronic form

   c. time of filing/furnishing

   [ ] contained in the international application as filed

   [ ] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purposes of search and/or examination

   [X] received by this Authority as an amendment* on 5 November 2004

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **1-21**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-21**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-21**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: WO 2001/000677 A
D2: WO 2002/051993A

The invention is to methods for the prophylaxis or treatment of cancer cells including circulating blood cell cancer, by blocking mitogen activated protein kinase (MAPK)-integrin binding interactions with an agent comprising a polypeptide that binds to a binding domain of the MAPK for a β integrin subunit wherein the β integrin subunit is not necessarily expressed by the cancer cells. The invention includes a composition of the said polypeptide and a signal peptide which acts to facilitate the passage of the agent across the outer cell membrane into the cancer cells. The signal peptide comprises the amino acid sequence AAVALLPAVLLALLA or AAVALLPAVLLALLAP and the polypeptide is selected from the following group; RSKAKWQTGTNPYR, RARAKWDTANNPLYK, RSRARYEMASNPLYR, RSKAKNPLYR, RARAKNPLYK, RSRARNPLYR, KEKLKSQWNNDNPLFK and KEKLKNPLFK.

Novelty (N): Claims 1-21

D1 and D2 each teaches methods of modulating integrin mediated cellular activity using agents capable of inhibiting the binding of MAPK to a binding domain of an integrin, thereby resulting in the inhibition of the growth of cancer cells. The agent or polypeptide is disclosed as comprising a fragment of an integrin subunit and includes the following amino acid sequences, RSKAKWQTGTNPLYR, RSKAKNPLYR, RSKAK or NPLYR. Carrier peptides for transporting delivery of the agent or polypeptide are also taught.

The present invention is distinguished over the prior art in that it was observed that it is not necessary for the integrin to which the MAPK binds to be expressed by the target cells in order to inhibit growth of the cancer cells. Common general knowledge in the art suggests that MAPK were activated remotely from the plasma membrane downstream of integrin transmembrane signalling and did not associate with integrin. D1 and D2 are directed to the finding that MAPK can bind to integrins. In seeking a method for the prophylaxis or treatment of cancer, the skilled addressee would focus on inhibiting the physical association of the MAPK with the integrin in order to down-regulate the activation of MAPK, thus requiring that the target cancer cells express the integrin. The present invention relates to the administration of a polypeptide that binds to a binding domain of a MAPK for a corresponding binding domain of a β integrin subunit in the treatment of cancer, wherein the β integrin subunit is essentially not expressed by the cancer cells. As such the claims 1-21 meet the criteria set forth in PCT Article 33(2) for novelty.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V

Inventive Step (IS): Claims 1-21

As above

Industrial Applicability (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

The term "polypeptide" is used interchangeably herein with "peptide" and encompasses amino acid sequences incorporating only a few amino acid residues or many amino acid residues coupled by peptide bonds. For instance, it will be understood that agents such as RSKAKNPLYR (SEQ ID No: 7) and KEKLKNPLFK (SEQ ID No: 10) fall within the scope of the term.

Typically, a polypeptide of the invention or administered to a mammal in accordance with the invention will have a length of about 150 amino acids or less, more preferably about 75 amino or 50 amino acids or less and most preferably, about 40 amino acids or less. When the polypeptide is a fusion protein or agent incorporating a carrier moiety, the binding moiety that binds to the integrin will generally have a length of between about 5 to about 50 amino acids and more preferably, a length of between about 5 to about 35 amino acids. Preferably, the polypeptide will have a length of up to 20 amino acids, more preferably a length of greater than 5 and up to 15 amino acids and most preferably, from 10 to 15 amino acids.

The binding domain of an integrin to which a MAP kinase binds or the binding domain of the MAP kinase for the integrin may be identified and characterised using protocols and techniques described in International Patent Application No. WO 01/000677 and International Patent Application No. WO 02/051993, the disclosures of both of which are expressly incorporated herein by reference in their entirety.

More specifically, a binding domain may be localised by assessing the capacity of respective overlapping peptide fragments of the cytoplasmic domain of an integrin subunit or from a MAP kinase to bind with the MAP kinase or integrin, respectively. The specific amino acid sequence which constitutes the binding domain may then be determined utilising progressively smaller peptide fragments. In particular, test peptides are readily synthesised to a desired length involving deletion of an amino acid or amino acids from one or both of the N-terminal and C-terminal ends of the larger amino acid sequence, and tested for their ability to bind with the MAP kinase or the integrin. This process is repeated until the minimum length peptide capable of binding with the MAP kinase or the integrin substantially without compromising the optimum observed level of binding is identified.

The identification of amino acids that play an active role in the MAP kinase integrin interaction may be achieved with the use of further synthesised test peptides in which one or more amino acids of the sequence are deleted or substituted with a different amino acid or amino acids to determine the effect on the ability of the peptide to bind with the MAP kinase or the integrin. By deletion in this context is meant deletion of one or more of the amino acids between the N-terminal and C-terminal amino acid residues of the identified binding

CLAIMS

1. A method for prophylaxis or treatment of a cancer in a mammal, wherein cancer cells of the cancer express a MAP kinase and the method comprises treating the mammal with an effective amount of a polypeptide that binds to a binding domain of the MAP kinase for a cytoplasmic binding domain of a β integrin subunit for the MAP kinase, and the β integrin subunit is essentially not expressed by the cancer cells.

2. A method according to claim 1 wherein the polypeptide comprises the binding domain of the β integrin subunit for the MAP kinase.

3. A method according to claim 1 wherein the polypeptide comprises a modified amino acid sequence compared to the binding domain of the β integrin subunit and the modified amino acid sequence has sufficient amino acid sequence homology with the binding domain of the β integrin subunit to bind to the binding domain of the MAP kinase.

4. A method according to claim 3 wherein the modified amino acid sequence comprises the binding domain of the β integrin subunit in which one or more amino acids in a linker region of the binding domain non-essential for the binding of the MAP kinase have been deleted.

5. A method according to claim 4 wherein the linker region of the binding domain has been deleted in the modified amino acid sequence.

6. A method according to claim 4 or 5 wherein the linker region binds opposite end regions of the binding domain of the β integrin subunit together and the end regions are unchanged in the modified amino acid sequence compared to the binding domain of the β integrin subunit.

7. A method according to claim 4 or 5 wherein the modified amino acid sequence has at least 50% overall amino acid sequence homology with the binding domain of the β integrin subunit.

8. A method according to claim 1 or 2 wherein the polypeptide is selected from the group consisting of RSKAKWQTGTNPLYR (SEQ ID No: 4), RARAKWDTANNPLYK (SEQ ID No: 5), RSRARYEMASNPLYR (SEQ ID No: 6), RSKAKNPLYR (SEQ ID No: 7), RARAKNPLYK (SEQ ID No: 8), RSRARNPLYR (SEQ ID No: 9), KEKLKSQWNNDNPLFK (SEQ ID No: 11) and KEKLKNPLFK (SEQ ID No: 10).

9. A method according to any one of claims 1 to 8 wherein the polypeptide is coupled to a facilitator moiety that facilitates passage of the polypeptide across the outer cell membrane of the cancer cells.

10. A method according to claim 9 wherein the facilitator moiety comprises a signal peptide, or a partial sequence or a modified form thereof.

11. A method according to claim 10 wherein the signal peptide is a signal peptide for a growth factor.

12. A method according to claim 10 or 11 wherein the signal peptide comprises the amino acid sequence AAVALLPAVLLALLA (SEQ ID No: 1).

13. A method according to claim 10 or 11 wherein the signal peptide comprises the amino acid sequence AAVALLPAVLLALLAP (SEQ ID No: 3).

14. A method according to any one of claims 1 to 13 wherein the polypeptide has a length of greater than 5, and up to 15, amino acids.

15. A method according to claim 14 wherein the polypeptide has a length of from 10 to 15 amino acids.

16. A method according to any one of claims 1 to 15 wherein the β integrin subunit is selected from the group consisting of β2, β3, β5 and β6.

17. A method according to claim 16 wherein the β integrin subunit is β6.

18. A method according to any one of claims 1 to 17 wherein the MAP kinase is selected from the group consisting of extracellular signal-regulated kinases (ERKs).

19. A method according to claim 18 wherein the MAP kinase is ERK2.

20. A method according to any one of claims 1 to 19 wherein the polypeptide is administered subcutaneously to the mammal for contact with the cancer cells at a site remote from the site of administration of the polypeptide.

21. A method according to any one of claims 1 to 20 wherein the cancer is selected from the group consisting of epithelial cell cancers, prostate cancer, lymphomas, blood cell cancers, leukemias, and cancer of the liver, tongue, salivary glands, gums, floor and other areas of the mouth, oropharynx, nasopharynx, hypopharynx and other oral cavities, oesophagus, gastrointestinal tract, stomach, small intestine, duodenum, colon, rectum, gallbladder, pancreas, larynx, trachea, bronchus, lung, breast, uterus, cervix, ovary, vagina, vulva, prostate, testes, penis, bladder, kidney, thyroid, and skin.

22. A method according to any one of claims 1 to 21 wherein the cancer is an epithelial cell cancer.

SEQUENCE LISTING

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